View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

ACC.15
TCT@ACC-i2 | innovation in intervention

A159
JACC March 17, 2015
Volume 65, Issue 10S

Acute Coronary Syndromes

NVP019 POTENTLY INHIBITS CYCLOPHILIN D-DEPENDENT MITOCHONDRIAL PERMEABILITY TRANSITION IN HUMAN HEART AND REDUCES MYOCARDIAL INFARCT SIZE IN MICE

Poster Contributions
Poster Hall B1
Sunday, March 15, 2015, 9:45 a.m.-10:30 a.m.

Session Title: Acute Coronary Syndromes: Basic
Abstract Category: 1. Acute Coronary Syndromes: Basic
Presentation Number: 1176-090

Authors: *Bruno Pillot, Sarah Piel, François Derimay, Abdallah Gharib, Magnus J. Hansson, Michel Ovize, UMR1060 (CarMeN-Team Cardioprotection), University Claude Bernard Lyon1, Lyon, France, NeuroVive Pharmaceutical AB, Lund, Sweden*

Background: Opening of the mitochondrial permeability transition pore (PTP) plays a key role in lethal myocardial reperfusion injury. Cyclophilin D (CypD) is a mitochondrial matrix protein that triggers PTP opening upon calcium accumulation at the time of reperfusion. The currently available cyclophilin inhibitor cyclosporin A (CsA) has some potential drawbacks including immunosuppression and several drug interactions. Our aim was to determine whether NVP019, a new non-immunosuppressive cyclophilin inhibitor with minimal off-target effects, might limit PTP opening, blunt lethal reperfusion injury and reduce infarct size.

Methods and Results: Anesthetized mice underwent 45 minutes of coronary artery occlusion followed by 24 hours of reperfusion. Area at risk (AAR) was assessed by blue dye injection and infarct size (IS) by triphenyltetrazolium chloride staining. Mice received either NVP019 (10 mg/kg) or vehicle (saline), administered as an IV bolus 5 minutes prior to reperfusion (n=9-10/group). In additional experiments, mitochondria were isolated from the risk region at the end of reperfusion and PTP opening was assessed in vitro by measuring the calcium retention capacity (CRC)(n=5/group). Further, PTP was analyzed in mitochondria isolated from CypD-KO mice as well as human atrial and ventricular tissue samples. AAR was comparable among groups. NVP019 reduced IS from 48±7% in control to 36±8% of AAR ($p<0.01$), and increased CRC that averaged 935±114 vs 469±52 nmoles Ca2+/mg prot in control ($p<0.0001$). Importantly, NVP019 demonstrated similar potency in inhibiting PTP in both rodent and human heart mitochondria (IC50 4-6 nM), but did not further increase the CRC in mitochondria isolated from CypD-KO mice hearts.

Conclusion: NVP019 reduces myocardial infarct size likely by the inhibition of PTP opening in a CypD-dependent manner.